

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:
OGILVY RENAULT LLP/S.E.N.C.R.L.,S.R.L.
1600 - 45 O'Connor Street
OTTAWA, Ontario
Canada, K1P 1A4

Date of mailing 27 July 2005 (27-07-2005)
(day/month/year)

Applicant's or agent's file reference
13453-62PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/CA2005/000472

International filing date (day/month/year)
30 March 2005 (30-03-2005)

Priority date (day/month/year)
30 March 2004 (30-03-2004)

International Patent Classification (IPC) or both national classification and IPC
IPC(7): A61K 39/395, A61P 37/00, A61K 39/00

Applicant
CANADIAN BLOOD SERVICES ET AL

1. This opinion contains indications relating to the following items :

- | | |
|--|--|
| <input checked="" type="checkbox"/> Box No. I | Basis of the opinion |
| <input checked="" type="checkbox"/> Box No. II | Priority |
| <input checked="" type="checkbox"/> Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> Box No. VI | Certain documents cited |
| <input type="checkbox"/> Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> Box No. VIII | Certain observations on the international application |

*Written Opinion due
on docket Jan. 30/06
NB.*

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Date of completion of this opinion
9 June 2005 (09-06-2005)

Authorized officer
Qianfa Chen (819) 994-1374

Box No. I **Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form

☐ furnished subsequently to this Authority for the purposes of search.

3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

Box No. II **Priority**

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary :

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

☐ the entire international application

☒ claim Nos. 1-29, 46, 48, 54 and 56

because:

☒ the said international application, or the said claim 1-29, 46, 48, 54 and 56 relate to the following subject matter which does not require an international search (*specify*) :

Claims 1-29, 46, 48, 54 and 56, which encompass a method of treatment of the human/animal body, are not required to be searched nor is an international preliminary examination required by this Authority under Rule 67.1(iv) PCT. Regardless, this Authority has established a written opinion based on the alleged effects of the products defined in claims 1-29, 46, 48, 54 and 56.

☐ the description, claims or drawings (*indicate particular elements below*) or said claim are so unclear that no meaningful opinion could be formed (*specify*) :

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>3- 6, 9, 10, 21-24, 26, 27, 33, 35, 36, 38- 42, 48-50, 53 and 54</u>	YES
	Claims	<u>1, 2, 7, 8, 11-20, 25, 28-32, 34, 37, 43-47, 51, 52, 55 and 56</u>	NO
Inventive step (IS)	Claims	<u>3, 5, 6, 9, 10, 21, 23, 24, 26, 33, 35, 36, 38, 48, 50 and 53</u>	YES
	Claims	<u>1, 2, 4, 7, 8, 11-20, 22, 25, 27-32, 34, 37, 39-47, 49, 51, 52 and 54-56</u>	NO
<u>Industrial applicability (IA)</u>	Claims	<u>1-56</u>	<u>YES</u>
	Claims		<u>NO</u>

2. Citations and explanations :

Reference is made to the following documents:

D1: WO 99/03495 A1 (AVRAHAM, H. and GROOPMAN J.E.), 28 January 1999.

D2: WO 02/40047 A2 (LAZARUS, A. et al.), 23 May 2002.

D3: SONG, S. et al. Blood. 1 May 2003. Vol.101, No.9, pages 3708-3713.

D4: CA 2,253,058 A1 (MADIYALAKAN, R. et al.), 02 March 2000.

D5: WO 02/076384 A2 (SCHULTES, B. and NICODEMUS, C.F.), 3 October 2002.

D1 (AVRAHAM, H. and GROOPMAN J.E.) describe the therapeutical application of a class of murine monoclonal antibodies (e.g., BAH-1 and M4 monoclonal antibodies), that is capable of stimulating proliferation of primary bone marrow megakaryocytes, for the preparation of a composition for treating, e.g., thrombocytopenia. The monoclonal antibody BAH-1 specifically recognizes the c-Mpl receptor on the surface of human and murine megakaryocytic cells. A typical composition comprises a therapeutically effective amount of BAH-1 monoclonal antibodies in association with a pharmaceutically acceptable carrier vehicle. An effective serum dosage of the antibody composition may be in the range of from about 1 to about 100 µg/ml, and preferably 10 µg/ml, resulting in about 1 mg/kg patient body weight.

D2 (LAZARUS, A. et al.) describes a method utilizing monoclonal intravenous immunoglobulin (e.g., an anti-red blood cell antibody, such as anti-CD24 or anti-TER-119, or an anti-leukocyte antibody, such as anti-CD44) for treating a disease known as auto-immune thrombocytopenic purpura (ITP). LAZARUS, A. et al. also describe a therapeutic composition comprising a therapeutic amount of at least one monoclonal intravenous immunoglobulin and a pharmaceutically acceptable carrier, said therapeutic amount being sufficient to increase platelet cell counts. The therapeutic amount of the monoclonal intravenous immunoglobulin administered preferably ranges from about 1 µg to about 1 g per kg of body weight per day.

(Continuation on Supplemental Box)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

D. Claim Defects

Claims 1, 17, 30, 43 and 44 are broader in scope than the teaching of the description and do not comply with Article 6 of the *Patent Cooperation Treaty (PCT)*. The claimed method, composition and use thereof encompass subject matter that is not contemplated in the description by the applicant. The instant description on page 14, lines 17-19 indicates that ovalbumin (OVA, a foreign antigen) incubated with anti-OVA antibodies was capable of inhibiting ITP. However, the instant description on page 14, lines 20-26 also describes that "mice treated with soluble OVA alone (Figure 3A&B, 0.0 mg/mouse) or OVA + control IgG (data not shown) were not significantly protected from the development of immune thrombocytopenia. OVA by itself did not affect the platelet count at any dose tested (0.1 mg, 1 mg, 5 mg and 10 mg, data not shown). Similarly, all of the anti-OVA antibodies, in the absence of OVA, did not inhibit immune thrombocytopenia (data not shown)". This clearly suggests that neither a foreign antigen in the absence of an antibody specific thereto, nor an antibody specific for a soluble foreign antigen in the absence of the foreign antigen is capable of treating ITP. The expression "an antibody specific for a soluble antigen" referred to in claims 1, 17, 30, 43 and 44 is held to encompass "an antibody specific for a soluble foreign antigen" and "an antibody specific for a soluble endogenous antigen". Therefore, a claim to a method or composition for treating ITP by administering an effective amount of an antibody specific for a soluble foreign antigen, without defining that the antibody specific for the soluble foreign antigen is incubated with the soluble foreign antigen prior to the administering, is not supported in the description as filed.

Claims 1, 14, 30, 43 and 44 are broader in scope than the teaching of the description and do not comply with Article 6 of the *Patent Cooperation Treaty (PCT)*. The description has only described that anti-OVA (in the presence of the antigen), anti-albumin, or anti-transferrin antibodies are capable of ameliorating ITP and arthritis. The description has not demonstrated that any other autoimmune diseases other than ITP and arthritis can be treated by any of the antibody treatment regimes. Therefore, the description fails to provide sufficient support for a method or composition of treating an autoimmune disease other than ITP or arthritis.

Claims 30 and 43 do not comply with Article 6 of the *Patent Cooperation Treaty (PCT)* because claims 30 and 43 are duplicative and therefore they are lacking conciseness.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V (page 1 of 2)

D3 (SONG, S. et al.) describes a method for ameliorating immune thrombocytopenia in a murine model of immune thrombocytopenic purpura comprising administering to the mice monoclonal antibodies (e.g., anti-TER-119 and anti-CD24 antibodies) with specificity for erythrocytes, and monoclonal antibodies (e.g., anti CD16/32 and anti-CD44 antibodies) directed against nonerythrocyte antigens.

D4 (MADIYALAKAN, R. et al.) describes a method and composition for treating a disease (e.g., autoimmune hemolytic anemia, and rheumatoid arthritis) by altering the immune response comprising administering a binding agent (e.g., an antibody) that specifically binds to a pre-selected soluble antigen (i.e., an antibody-antigen complex).

D5 (SCHULTES, B. and NICODEMUS, C.F.) describes a method and composition for generating both a humoral and/or a cellular immune response by administering a binding agent (e.g., an antibody) that specifically binds to a pre-selected soluble antigen. The binding agent-soluble antigen complex alters the immunogenic condition of the host such that the immunogenicity of the antigen is increased or decreased in a manner that produces a beneficial or therapeutically desirable effect (e.g., for treating cancer or autoimmune disease such as rheumatoid arthritis).

A. Novelty

Claims 1, 2, 7, 11-15, 17-20, 25, 28-32, 37, 43-47, 51, 52, 55 and 56 lack novelty and do not comply with Article 33(2) of the *Patent Cooperation Treaty (PCT)*, as being anticipated by D1 while claims 1, 7, 11-15, 17-19, 25, 28-31, 43-46, 51, 52, 55 and 56 lack novelty and do not comply with Article 33(2) of the Patent Cooperation Treaty (PCT), as being anticipated D2 or D3. D1, D2 and D3 have separately described a method and composition for treating immune thrombocytopenic purpura (ITP) or for increasing and maintaining platelet cell counts by administering an effective amount of at least one antibody (e.g., the anti-c-Mpl antibody in D1, and the anti-CD24 and anti-CD44 antibodies in D2 and D3). Although majority of each of the proteins of c-Mpl, CD24 and CD44 are present on the cell surface, the soluble form of each of the proteins of c-Mpl, CD24 and CD44 has been either prepared or detected previously in the art (e.g., KUTER, D. and ROSENBERG, R.D. Blood. 15 May 1995. Vol.85, No.10, pages 2720-2730; AIGNER, S. et al. FASEB J. September 1998. Vol.12, No.12, pages 1241-1251; and RISTAMAKI, R. et al. Blood. 1 July 1994. Vol.84, No.1, pages 238-243). Therefore, the anti-c-Mpl antibody in D1, and the anti-CD24 and anti-CD44 antibodies in D2 and D3 fall within the scope of an antibody specific for a soluble antigen. Further, the monoclonal anti-c-Mpl antibody in D1 specifically recognizes the c-Mpl receptor antigen present on the surface of both human and murine megakaryocytic cells. In relation to the human cells, the murine c-Mpl receptor antigen is a foreign antigen. Therefore, the anti-c-Mpl antibody in D1 falls within the scope of an antibody specific for a foreign antigen.

Claims 1, 7, 8, 11-14, 16, 30, 34, 43 and 44 lack novelty and do not comply with Article 33(2) of the *Patent Cooperation Treaty (PCT)*, as being anticipated by D4 or D5. D4 or D5 has separately described a method and composition for treating a disease (e.g., autoimmune hemolytic anemia, and rheumatoid arthritis) by administering an effective amount of antibody-antigen complex that is prepared, prior to the administering, by incubating a soluble antigen and a specific antibody thereto. Therefore, D4 or D5 appears to be novelty destroying for the subject matter of claims 1, 7, 8, 11-14, 16, 30, 34, 43 and 44.

Claims 3-6, 9, 10, 21-24, 26, 27, 33, 35, 36, 38-42, 48-50, 53 and 54 meet the criteria set out in Article 33(2) of the Patent Cooperation Treaty (PCT), because the closest prior art (D1, D2, D3, D4 or D5) does not teach the specific technical features of these claims.

(Continuation on Supplemental Box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V (page 2 of 2)

B. Inventive Steps

Claims 4, 22, 39-42 and 49 lack an inventive step and do not comply with Article 33(3) of the *Patent Cooperation Treaty (PCT)*. D1 has described a method and composition for treating immune thrombocytopenic purpura (ITP) or for increasing and maintaining platelet cell counts by administering an effective amount of at least one antibody specific for a soluble foreign antigen. D4 or D5 has separately described a method and composition for treating a disease (e.g., autoimmune hemolytic anemia, and rheumatoid arthritis) by administering an effective amount of antibody-antigen complex wherein the antibody-antigen complex alters the immunogenic condition of the host such that the immunogenicity of the antigen is increased or decreased in a manner that produces a beneficial or therapeutically desirable effect. Therefore, it would be obvious to a person skilled in the art to substitute the antibody of D1 for the antibody-antigen complex of D4 or D5 thereby arriving at the subject matter of claims 4, 22, 39-42 and 49. Thus, claims 4, 22, 39-42 and 49 lack inventive steps in light of teaching of D1 in combination with D4 or D5.

Claims 27 and 54 lack an inventive step and do not comply with Article 33(3) of the *Patent Cooperation Treaty (PCT)*. D1, D2 or D3 has separately described a method and composition for treating immune thrombocytopenic purpura (ITP) or for increasing and maintaining platelet cell counts by administering an effective amount of at least one antibody specific for a soluble endogenous antigen. D4 or D5 has separately described a method and composition for treating a disease (e.g., autoimmune hemolytic anemia, and rheumatoid arthritis) by administering an effective amount of antibody-antigen complex wherein the antibody-antigen complex alters the immunogenic condition of the host such that the immunogenicity of the antigen is increased or decreased in a manner that produces a beneficial or therapeutically desirable effect. Therefore, it would be obvious to a person skilled in the art to substitute the antibody of D1, D2 or D3 for the antibody-antigen complex of D4 or D5 thereby arriving at the subject matter of claims 27 and 54. Thus, claims 27 and 54 lack inventive steps in light of teaching of D1, D2 or D3 in combination with D4 or D5.

Claims 3, 5, 6, 9, 10, 21, 23, 24, 26, 33, 35, 36, 38, 48, 50 and 53 involve an inventive step and meet the criteria set out in Article 33(3) of the *Patent Cooperation Treaty (PCT)*, because none of the prior art describes a method or composition for treating ITP by administering an effective amount of anti-ovalbumin, anti-albumin and anti-transferrin antibodies.

C. Industrial Applicability

Claims 1-29, 46, 48, 54 and 56 appear to define subject matter that has industrial applicability under Article 33(4) of the PCT, based on the function of the agents and compositions of the instant application for treating immune thrombocytopenic purpura or for inhibiting platelet clearance in a patient. Although the methods per se defined in claims 1-29, 46, 48, 54 and 56 relate to subject matter which this Authority is not obliged to examine under Rule 67.1 (iv) of the PCT, the use of the aforementioned agents and compositions referred to therein for treating immune thrombocytopenic purpura or for inhibiting platelet clearance in a patient appears to represent subject matter that has industrial applicability.

Claims 30-45, 47, 49-53 and 55 have industrial applicability as defined under Article 33(4) of the *Patent Cooperation Treaty (PCT)*.